UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' *DAUBERT* MOTION TO PRECLUDE CERTAIN OPINIONS OF PLAINTIFFS' EXPERT RAMIN (RON) NAJAFI, PH.D.

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

STATUTES and REGULATIONS:

CASES CITED:

INTRODUCTION

Dr. Najafi is a Ph.D. chemist with over 30 years of experience in the pharmaceutical industry. He has held several scientific roles at companies such as Rhone Poulenc Rorer (now Sanofi-Aventis), Applied Biosystems – a division of Perkin Elmer (now Thermo Fisher), and Aldrich Chemical Company (now Millipore Sigma). [redacted] **Exhibit A to the Certification of Rosemarie Riddell Bogdan** and hereinafter referred to throughout as **Najafi Rpt.** (Note: All bolded **"Exhibits"** noted herein are attached to the Certification of Rosemarie Riddell Bogdan which is accompanying this motion). In these roles, Dr. Najafi gained extensive experience in all aspects of pharmaceutical and chemical development, spanning from the R&D stage to pilot plant manufacturing and outsourcing of the manufacture of active pharmaceutical ingredients (APIs). [redacted] Dr. Najafi currently is the Chairman and CEO of Emery Pharma, a FDA registered and inspected, CGMP / GLP compliant research laboratory which does work for pharmaceutical companies developing drugs for FDA approval. [redacted] Thus, Dr. Najafi has extensive experience with pharmaceutical drug development and manufacture, knows the requirements of current good manufacturing practices in the pharmaceutical industry, and has a broad knowledge of the guidances and regulations that are considered by the industry when developing good manufacturing practices. [redacted] One does not need to be a former employee of or consultant for the FDA or have worked in "regulatory affairs" for a "generic drug manufacturer" [redacted]

[redacted] The assertion that Dr. Najafi is not qualified to offer opinions in these areas is belied by the facts.

In addition to being well-qualified, Dr. Najafi relies on basic chemistry principles, scientific literature, and defendants' documents and testimony, [redacted] This is a reliable methodology and provides a sound basis for his opinions.

Defendants also mischaracterize the record. [redacted]

Defendants include additional criticisms, none of which are of any consequence. Dr. Najafi is not offering improper legal opinions. [redacted]

[redacted]

[1] [redacted]

[2] [redacted]

[3] See https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis valsartan-products.

[redacted]

APPLICABLE LEGAL STANDARD

"Under the Federal Rules of Evidence, a trial judge acts as a 'gatekeeper' to ensure that 'any and all expert testimony or evidence is not only relevant, but also reliable.'" *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008) (citation omitted). Rule 702, the rule that governs expert testimony, has a "liberal policy of admissibility." *Id.* In essence, the expert testimony must meet the following requirements: "(1) the proffered witness must be an expert, i.e., must be qualified; (2) the expert must testify about matters requiring scientific, technical or specialized knowledge; and (3) the expert's testimony must assist the trier of fact." *Id.* at 244.

POINT ONE

DR. NAJAFI HAS A RELIABLE BASIS TO OPINE [redacted] Defendants' brief, p. 4 – "Defendants do not seek

to exclude that testimony.” [redacted]

Importantly, the first principle of risk assessment - the identification of hazards – is spelled out by the FDA [redacted]; See also *FDA Guidance for Industry, Q9 Quality Risk Management (June 2006*) at p.4. https://www.fda.gov/media/71543/download. Risk assessment involves the systematic use of information to identify hazards. That information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. *Id*. Quality Risk Management provides a proactive approach to identifying, evaluating and controlling potential risks to quality and integral to this function is “knowledge management” which

is a systematic approach to acquiring and analyzing prior knowledge relating to manufacturing processes. See *FDA Guidance for Industry, ICH Q10, Pharmaceutical Quality System (April 2009),* p. 4. https://www.fda.gov/media/71553/download. In essence, chemical risk assessment involves identification of potential risks based on the chemicals used in the process, known chemical reactions and theoretical analysis.

[redacted]

[redacted]

A. [redacted]

[redacted] [redacted] [redacted]

[redacted]

[redacted]

[redacted] Notably, an opinion based on general experience, scientific knowledge of chemicals and universal chemical reaction principles is admissible under *Daubert*, without a requirement that specific literature be cited. See *Westley v. Ecolab, Inc. 2004 WL 1068805; 2004 U.S. Dist. LEXIS 9936; (D.C.Pa. 2004).* [redacted]

[redacted]; *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 17*, *Some N-nitroso compounds, pp 83-175, Lyon, France (1978)* at page 36. https://publications.iarc.fr/35. This same peer-reviewed **1978** monograph, the purpose of which is to collect all relevant

experimental and epidemiological data available at the time, speaks to "nitrosatable substance that occur in the environment include secondary and tertiary amines" *Id.* at Monograph Introduction page (unnumbered), 37 and 40. As such, this **1978** publication, which cites to even earlier studies, [redacted]

[redacted] *Smith & Loeppky (**1967**), Nitrosative cleavage of tertiary amines, J. Am. Chem. Soc. 89. 1147-1157; Lijinsky, W., Keefer, L., Conrad, E. & Van De Bogart, R. (**1972**) Nitrosation of tertiary amines and some biological implications. J. Natl. Cancer Inst., **49,** 1239-1249; and Challis, B.C. & Shuker, D.E.G. (**1979**) Rapid nitrosation of amines in aqueous alkaline solutions by B-substituted alkyl nitrites. J. Chem. Soc. Chem. Commun. 315-316*

[redacted]

B. [redacted]

[redacted]

[redacted]

[6] [redacted], *Purification of Laboratory Chemicals, Armarego, WLF (4th Edition **1996**; 6th Edition **2009**) at p.192* - **Exhibit K**.
[7] *Id. at p.192.*

[redacted]

[redacted]

[8] [redacted]

[redacted]

[redacted]

[redacted]

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9 [redacted]

[redacted][10]

[redacted]

POINT TWO

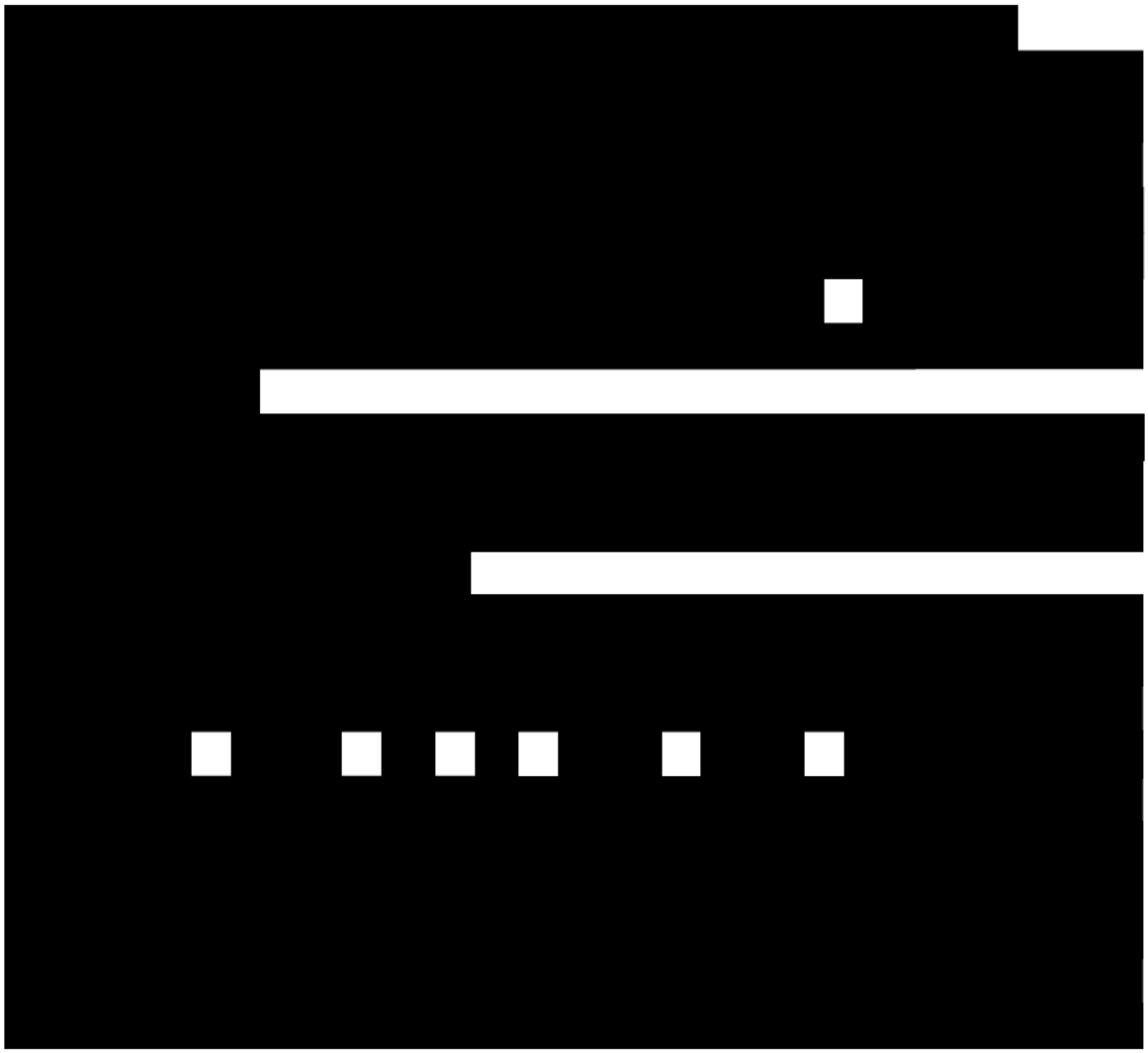
[redacted]

A. [redacted]

[10] [redacted]

[11] [redacted], Loeppky et al. entitled *Ester-Mediated Nitrosamine Formation From Nitrite and Secondary or Tertiary Amines,* IARC Sci. Publ. 57, 353-363 (1984). [redacted]

[redacted]



[redacted]

The report was more than sufficient to raise the issue. In fact, it is well established that Courts allow opinions expressed by an expert at deposition that are reasonably said to be well-within the scope of an expert's report even if the report doesn't use the same words verbatim. *Ouelette v. Coty US, LLC*, 2016 WL 1650775; 2016 US Dist. LEXIS 54651 (M.D. Pa., 2016). The Third Circuit has even allowed expert testimony where there is a "slight deviation from pre-trial notice requirements and admitting the witness [is] likely to cause only slight prejudice" to an opposing party who was already aware of the "basic substance of the witness' testimony." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 792 (3d Cir. 1994) (citing *DeMarines v. KLM Royal Dutch Airlines*, 580 F.2d 1193, 1202 (3d Cir. 1978). Since the issue was in the report, there is no such issue.

The case cited by defendants, *Krys v. Aaron,* 112 F.Supp.3d 181, 207 (D.N.J., 2015), is completely inapposite to the present case as it precluded an accounting expert from testifying about a 2002 financial statement when his expert report only analyzed the 2003 and 2004 financial statements. [redacted]

B. [redacted]

[redacted] when there is a valid scientific connection to the inquiry without too great an analytical gap between the data and the opinion. *Soldo v. Sandoz Pharms. Corp*., 244 F.2d 434 (W.D. Pa., 2003). [redacted]

Dr. Najafi's opinions certainly "fit" the central questions in this litigation and have a valid scientific connection to the case. [redacted]

[redacted]

The defendants are free to cross-examine Dr. Najafi on this issue, if they choose, but there is simply no legitimate question of "fit" or helpfulness to the jury.

POINT THREE

[redacted]

A. [redacted]

[redacted] **over 30 years of experience** in the pharmaceutical industry. Since 1989, Dr. Najafi, a Ph.D. organic chemist who has taught advanced organic synthesis, has worked in the pharmaceutical industry beginning his career with Aldrich Chemical Company as a Senior Development Chemist and Rhone Poulenc Rorer, the predecessor company of Sanofi-Aventis, as a Research Scientist. [redacted] In these roles, Dr. Najafi lead a team of chemists responsible for the research and development

[12] [redacted]

of new products, including synthesizing drug candidates in accordance with current good manufacturing practices (cGMP). [redacted] After working for pharmaceutical companies, Dr. Najafi founded several companies, one of which was Novabay, where he developed an investigational drug (NV-422) and met with the FDA several times regarding the investigation of the new drug. [redacted] compliant contract research laboratory. Emery Pharma conducts both research and development (R&D) work, and cGMP compliant work for pharmaceutical companies following regulatory guidance of the FDA, ICH and USP. [redacted] Dr. Najafi works with clients to submit new drug applications, abbreviated new drug applications, FDA filings and support in the drug development and approval process. [redacted] Emery Pharma tests drug compounds for official release for their pharmaceutical clients according to FDA guidances, ASP guidance or GMP/GLP guidance which includes identification of impurities. Dr. Najafi

and the other chemists at Emery use USP monographs in their work constantly. [redacted] Dr. Najafi and the other chemists at Emery Pharma are hired by pharmaceutical companies to identify impurities in drug products and conduct risk assessments for ANDAs and NDAs on a routine basis. [redacted] Dr. Najafi has developed the synthetic process of hundreds of molecules in his career. [redacted]

The qualification requirement of Rule 702 and *Daubert* is applied broadly and liberally. An expert, like Dr. Najafi, may be qualified through a "broad range of knowledge, skills and training" including academic credentials and practical experience. *In re Proton-Pump Inhibitor Prods. Liab. Litig*., 2022 WL 18999830; 2022 U.S. Dist. LEXIS 239870, *684-685 (D.N.J., 2022). For example, in *Yeazel v. Baxter Healthcare Corp. (In re Heparin Prod. Liab. Litig.)*, 2011 WL 1059660; 2011 U.S. Dist. LEXIS 36299 (N.D. OH., 2011), *7-9, the Court found a microbiologist and founder of a consultant firm involved with pharmaceutical development and manufacturing processes and with extensive experience at various pharmaceutical companies, to be qualified to opine on the processes involved in the manufacture of drugs, including quality control measures, protocols in dealing with suppliers and how to prevent contamination and adulteration, regarding the testing of ingredients and final products to confirm compliance with regulatory standards for purity and safety. *Yeazel*, at *7-9, 10-12.

The *Rheinfrank* case cited by defendants is not applicable here as the Court found a neurologist, geneticist and an epidemiologist, all without relevant experience, not qualified to opine on FDA regulatory compliance or what information should have been submitted to the FDA or what the label approved by the FDA should have included. *Rheinfrank v. Abbott Lab's, Inc.,* 680 F. App'x 369, 376, 381 (6th Cir., 2017).

Based on his education, wealth of practical experience and knowledge obtained from working in the pharmaceutical industry regarding risk assessments, identifications of impurities, cGMPs, CFRs, qualification of API suppliers, and regulatory guidances, [redacted]

It is recognized that an expert can opine on mixed questions of law and fact. For instance, in *Alto v. Sun Pharm. Indus*., 2021 WL 4803582; 2121 U.S. Dist. LEXIS 198390 (S.D.N.Y., 2021), a pharmaceutical expert was permitted to express opinions as to the industry standards and opinions on pharmaceutical industry standard practices and whether the defendant complied with that standard was acceptable even though the ultimate question of whether the conduct complied with the terms of a contract was left to the court or factfinder. *Id.* at 33-34.

The *Krys* Court summarized the Third Circuit's guidance on this issue, indicating that any qualified expert "may provide an opinion on whether a party's conduct or actions meet the underlying bases for an ultimate issue in a case (by, for example,

testifying concerning whether certain acts would in the abstract be improper and/or inconsistent with a party's legal duties), but may not merely instruct the jury on the result to reach based upon a party's specific conduct or actions (by, for example, stating that a party did indeed violate an applicable duty through certain actions)." *Krys v. Aaron*, 112 F. Supp.3d 181 at 193 (D.N.J., 2015).

This concept was also addressed in *Nature's Prods. v. Natrol, Inc*., 2013 WL 7738172; U.S. Dist. LEXIS 185676 at *9-12 (S.D. Fla., 2013) where an expert who was a Ph.D. in cereal science and technology with 13 years of food science company experience was found qualified to render opinions as to whether the adversary company had complied with FDA requirements by relying upon and citing relevant GMPs and academic literature. The Court found the expert to have a reliable methodology and by virtue of her experience, education, and overall expertise, was able to opine as to whether the manufacturing process comported with the applicable FDA GMPs. The opinions of this expert as to compliance with regulatory GMPs were not considered to be legal conclusions. *See also*, *Blue Cross Blue Shield Ass'n v. GlaxoSmithKline LLC*, 2019 WL 4751883, at *4, (permitting Mr. Russ to testify that, due to these chronic [cGMP] failures, GSK could not assure the At-Issue Drugs "conformed to their represented properties of safety, identity, strength, purity, and quality.") (internal quotation marks omitted); *Wolfe v. McNeil-PPC, Inc.*, 881 F.Supp.2d 650, 660 (E.D. Pa. 2012) (Experts permitted to testify regarding FDA regulations and regulation-related documents as such testimony will assist the trier of fact); *In re Yasmin & YAZ (Drospirenone) Mktg., Sales Practices & Prods. Liab. Litig.*, No. 09-2100, 2011 WL 6302287, at *25 (S.D. Ill. Dec. 16, 2011) ("To the extent [the expert] does offer legal

conclusions, the Court finds that [the expert's] testimony is permissible because of the complex nature of the process and procedures and the jury needs assistance understanding it. [The expert's] testimony will assist the trier of fact in understanding the federal regulations, and the jury will be instructed that the Court, not [the expert] nor any other witness, will instruct the jury on the law in this case."); *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164,191 (S.D.N.Y. 2009) (denying motion to preclude expert from "testifying about general FDA regulatory requirements and procedures or offering an opinion as to [the pharmaceutical company's] compliance therewith"); *Pfizer v. Teva Pharms. USA, Inc.*, 461 F. Supp. 2d 271, 278–79 (D.N.J 2006) (finding admissible expert testimony regarding FDA regulation of labeling, advertising, and promotion of prescription drugs, and to what extent firm complied with those requirements).

[redacted]

[redacted]

The cases cited by defendants are inapposite: *Decker v. GE Healthcare*, Inc., 770 F.3d 378 (6th Cir., 2014), (dermatologist not experienced in pharmacovigilance not allowed to testify to pharmacovigilance); *In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig.*, 2000 WL 876900; 2000 US Dist. LEXIS 9037 (Pa. E.D., 2000) (experts not familiar with FDA regulations governing warnings and labeling

[redacted]

could not testify to same); *Stanley v. Novartis Pharms. Corp.*, 2014 WL 12573393 (C.D. Cal., 2014) (expert cannot testify to intent, motives or states of mind of corporations or regulatory agencies, [redacted] *Terry v. McNeil-PPC, Inc. (In re Tylenol (Acetaminophen) Mktg., Sales Practices & Prods. Liab. Litig.),* 2016 WL 4039324, 2016 U.S. Dist. LEXIS 98858 (E.D. Pa., 2016) (only prevents a regulatory expert from opining whether Tylenol would legally be considered as Generally Recognized as Safe and Effective (GRASE), which required a legal interpretation of the meaning of GRASE but did allow the expert to testify to the legal framework governing acetaminophen products); *Berckeley Inv. Group, Ltd. v. Colkitt*, 455 F.3d 195 at 218 (3d Cir., 2006), (FRE 702 permits expert to give testimony that embraces ultimate issue but can't render legal opinion; however, "…the line between admissible and inadmissible expert testimony as to customs and practices of a particular industry often becomes blurred when the testimony concerns a party's compliance with customs and practices that implicate legal duties"…expert could give opinions "as to legal duties arising from industry custom").

POINT FOUR

[redacted]

[redacted]

The cases cited by defendants are easily distinguished. *Steele v. Aramark Corp*., 2012 WL 106879 (D.N.J. 2012), workers' compensation doctor not qualified on toxic kidney injuries due to toluene; *Godreau-Rivera v. Soloplast Corp*., 598 F. Supp. 3d 196 (D. Del., 2022), polymer biomaterials expert qualified to opine on polypropylene degradation *in vivo* but not its medical toxicity; *Cunningham v. Masterwear, Inc*., 2007 WL 1164832 (S. D. Ind., 2007), pulmonary doctor and treating medical doctor not qualified

[15] See Page 5 of *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), version May 2015, version March 2018*, https://www.fda.gov/media/85885/download

[16] [redacted] *EMA Guideline on the Limits of Genotoxic Impurities*, 1/2007-1/2018, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-limits-genotoxic-impurities_en.pdf; See *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, Guidance for Industry, FN 15*; *ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*, August 25, 2015, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m7r1-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit_en.pdf.

to opine on clinical toxicity dose of PCE; *Blanchard v. Eli Lilly & Co*., 207 F. Supp.2d 308 (D. Vt. 2002), psychiatrist qualified to opine on causes of suicide but method and supportive data used unreliable; S*utera v. Perrier Grp. Of Am. Inc*., 986 F. Supp. 655 (D. Mass. 1997), oncologist/hematologist with no experience in toxic agent causation not qualified; *Cooper v. Lab'y Corp. of Am. Holdings*, 150 F. 3d 376 (4th Cir., 1998) plaintiff's expert had only a "general knowledge of chemistry" and no training, experience or skill in the field of urine alcohol testing so not qualified to opine on urine testing]. Unlike the above cases, Dr. Najafi is an experienced organic chemist who has many years of education, expertise and knowledge of nitrosamines and their properties and is fully qualified for his opinions.

CONCLUSION

For the foregoing reasons, Defendants' motion to preclude certain of Dr. Najafi's opinions should be denied.

Respectfully submitted,
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CERTIFICATE OF SERVICE

I hereby certify that on April 11, 2023, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notifications of such filing to the CM/ECF participants registered to receive service in this MDL.

/s/ Rosemarie Riddell Bogdan

Rosemarie Riddell Bogdan